REMARKS

In the outstanding Office Action, the Examiner has claims 1-12 and 17-24 stand rejected under 35 U.S.C. 103(a) as being obvious over any of Kaufman, Leahy I et al., Leahy II et al. or Hayashi in view of Ogawa et al.

In the Office Action, the Examiner bases the above rejection on the conclusion that one of skill in the art would apply the teachings of glycoproteins to glycomacropeptides and vice versa.

Applicants respectfully disagree with this basis for rejecting the present claims and more particularly, the teachings of peptides and glycoproteins do not overlap as the Examiner is asserting especially in the case of the present invention.

It is well understood that peptides are the family of short molecules formed from the linking, in a defined order, of various amino acids. In contrast, proteins are polypeptide molecules (or consist of multiple polypeptide subunits). A clear distinction between the two is that peptides are short and proteins are long and therefore, there is a substantial difference in the structures between the two and further, this corresponds in different characteristics as to how the two behave differently from one another.

Moreover, the term glycoprotein covers a number of different proteins that fall within a class and in particular, glycoproteins are proteins that contain oligosaccharide chains covalently attached to their polypeptide side-chains. As stated above, since glycoproteins are proteins they are large, large molecules that have very large molecular weights and therefore behave in a certain way.

In rejecting the claims, the Examiner cites a number of documents that are limited to only teaching the use of glycoproteins in ophthalmic preparations. For example, Kaufman discloses a deep mucinous layer composed of glycoprotein mucin and Applicants' own patents (Leahy I and II) are only limited to the use of mucin which is a glycoprotein. The other references cited by the Examiner once again are limited to only teaching that glycoproteins can be used in ophthalmic preparations.

In discussing the Hayashi reference, the Examiner states that it is not known if the glycoprotein in Hayashi is also referred to as glycomacropeptide. However, this can not be the case since by definition, the two are completely different structures and cannot be equated. A glycomacropeptide is not a protein and vice versa. Once the Examiner appreciates this distinction and that the two have much different structures and characteristics and are formed in different ways, as discussed below, Applicants respectfully submit that the Examiner will appreciate that the teachings of one cannot be simply applied to the other.

In the present specification, the Applicants differentiate and draw distinctions between glycoproteins and glycomacropeptide (see paragraph [0035]). Mucin is a class of glycosylated proteins and is a mixture of **many high molecular weight proteins**, typically having molecular weights of 1,000,000 Daltons or greater. Mucins have no specific protein structure and can vary widely in the degree of glycosylation. Mucins are typically not water-soluble but form colloids and gels in an aqueous environment.

In contrast, the peptide commonly referred to as glycomacropeptide is only a peptide and therefore is a short molecule formed from linking various

amino acids. Glycomacropeptide is not be a protein since a peptide by definition is not a protein. Glycomacropeptide is derived from specific casein. Caseins are a class of proteins that are distinctly different from mucins and therefore caseins are not substitutes for mucins. Glycomacropeptide, as described in the present specification, is derived from kappa-casein, a very specific protein. When hydrolyzed at a specific point in the protein, two peptides are formed, para-k-casein is the larger and glycomacropeptide is the smaller fragment. Glycomacropeptide, has a very specific amino acid sequence, is low molecular weight (around 8,000 Daltons) and is water-soluble. The Examiner will appreciate that these characteristics clearly distinguish over the characteristics associated with glycoproteins as discussed above.

Glycomacropeptide is **not** a mixture of peptides but is **one peptide** having a very well defined structure. Glycomacropeptide as described above has totally different structural features from those of mucin. Applicants respectfully assert that one of skill in the art would agree that glycomacropeptide is not even in the same family as mucins. While mucins can be obtained from a variety of sources (including milk), glycomacropeptide can only be derived from kappa-casein.

The prior art references clearly teach that large molecule structures (glycoproteins) provide advantages when used in ophthalmic preparations; however, these references are silent as to the use of a *very specific, much smaller molecule* in an ophthalmic preparation, namely, glycomacropeptide. Glycomacropeptide is not capable of being derived from mucin and therefore, the references that are limited to the use of mucin do not address or even

contemplate that a specific peptide that is isolated from a completely different source can provide the advantages described in the present application. Applicants discovered that when properly processed to casein by-product can yield surprising results.

Applicants respectfully submit that one of skill in the art, when reading all of the references cited by the Examiner, is taught that large, complex protein molecules (mucin) provide a number of advantages when employed in ophthalmic preparations. The fact that all the references have this common theme supports this conclusion. As such, any substitution taught by the references would be between glycoproteins of different classes.

Applicants' own prior patents never mention glycomacropeptide for the simple reason that at that time, the focus was on providing a mucin component, similar to the one found at the normal human ocular surface and therefore, the focus was on large protein molecules. The other prior art references are similar in that the focus was on mimicking the human ocular surface and therefore, the focus was on proteins an in particular, mucins.

The reason that the references cited by the Examiner disclose glycoproteins (mucin) but all fail to disclose glycomacropeptide is that it is not at all obvious to equate mucins and glycomacropeptide since they are totally different in structure and class and in their origins. If as the Examiner suggests that the two biochemistry fields and classes are interchangeable, at least one of the references should have mentioned the use of glycomacropeptide. This is not the case.

Applicants have amended claim 1 to further clarify and distinguish the the use of glycomacropeptide. In particular, claim 1 recites that the

ophthalmic preparation includes a glycomacropeptide derived from casein that is found in one of mammalian milk and a milk byproduct. This makes clear that glycomacropeptide is a very specific peptide that only is derived from one structure (casein).

Since glycomacropeptide is not a mucin or even a protein nor can it be derived from mucin, the prior art references do not disclose its use in an ophthalmic preparation and there is simply no suggestion in the prior art references of substituting a very large molecular weight protein with a much smaller molecule that is not even a protein, namely, glycomacropeptide. If the references suggest anything it would be to substitute large molecular weight structures for other ones since the classes and structures are more similar. After much research, Applicants surprisingly discovered the usefulness of glycomacroprotein in the claimed preparation.

Based on the foregoing, Applicants respectfully submit that one of skill in the art would not be motivated to substitute a large, complex glycoprotein, such as mucin, with a very small, non protein structure, namely GMP.

Reconsideration and allowance of amended claim 1 are respectfully and earnestly solicited.

Claims 2-12 should be allowed as depending from what should be an allowed claim 1, as amended.

In addition, these claim further distinguish the present invention over the prior art references. For example, claim 3 recites that the glycomacropeptide is a soluble part of hydrolyzed casein that is isolated from other parts of the hydrolyzed casein. Applicants once again respectfully submit that none of the references, taken alone or in combination, disclose or

contemplate the use of a very specific peptide that needs to be isolated from a specific source (casein) which is unrelated to the specific structures cited by the Examiner in the outstanding rejection.

Claims 17-23 should be allowed for the same reasons as to why claim 1 should be allowed.

With respect to the rejections of claims 1-12 and 17-23 on the ground of nonstatutory obviousness-type double patenting, Applicants respectfully submit that these rejections should be withdrawn for the reasons discussed above in that glycomacropeptide should not be equated to glycoprotein and the references cited in this rejection are limited to teaching the use of glycoproteins. Withdrawal of these rejections are in order.

Applicants believe that the present communication is fully responsive and addresses each issue raised by the Examiner in the Office Action.

In view of the above amendment, Applicants believe the pending application is in condition for allowance.

It is believed that no fees are due or all fees have been paid; however, if the Patent Office believes that additional fees are due, the Patent Office is authorized to charge Deposit Account No. 50-4570 up to $600.00.

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